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ORIGINAL ARTICLE

Psychedelic innovations and the crisis of psychopharmacology

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Abstract

In the 2010s, psychopharmacological research and development experienced a crisis: since no genuinely new drugs for the treatment of mental illness had been successfully developed for decades, major pharmaceutical corporations decided to disinvest their neuropsychopharmacology departments. At the same time, however, one branch of psychopharmacology began to boom. The FDA declared psychedelic-assisted psychotherapy a breakthrough therapy and hundreds of start-up companies began to compete for this potentially emerging health care market. The article looks at the case of psychedelic research to examine three different responses to the innovation crisis in psychopharmacology: (1) the resumption of pharmacopsychotherapy as a half-century old but previously marginalized and discontinued practice; (2) the continuation of self-experimentation as a simultaneously repressed and revitalized method of drug development; (3) computational drug design as a cutting-edge approach currently used to create non-psychedelic psychedelics that reduce psychiatric symptoms without any mind-altering effects. These responses point to conflicting imaginaries of innovation that envisage the future of psychopharmacology and thereby provide different diagnoses of its current predicament.

Keywords Psychopharmacology · Psychedelics · Psychedelic therapy · Innovation · Rational drug design · Self-experiment

Introduction

Knowledge cultures undergo mood swings. It is not just individual researchers but whole research fields that feel up, down, or in crisis. It is difficult—although not impossible—for those who have entered these fields to escape from the prevailing atmosphere created by opinion leaders (Bude 2017). There are times when the future

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appears wide open and times when a field only seems to produce more of the same and its practitioners grow frustrated and bored. The affective dimension of research is experienced subjectively, but it reflects what is happening out there: conceptual shifts that offer fresh perspectives, insurmountable epistemic obstacles, stifling work conditions, or a widely shared sense of how much more or how little there is still to learn about the scientific object that originally aroused the researchers' cognitive passions.

In a nostalgic key, the 1950s and 1960s are known as the Golden Age of Psychopharmacology. They were a time of adventurous and sometimes reckless experimentation, great discoveries, high hopes, and moral panics. In less than two decades, drug researchers discovered the hallucinogen LSD (1943), the antipsychotics chlorpromazine (1951) and haloperidole (1958), the antidepressants imipramine (1951) and reserpine (1952), and the benzodiazepine chlordiazepoxide (1957) (Healy 2002). Most of these discoveries had been serendipitous: an accidental contamination followed by a deliberate self-experiment in the case of LSD (Hofmann 1983), in other cases chance observations of clinical benefits in psychiatric patients who had received the drug for treating one condition only to find that it helped against a different one (Klein 2008). These findings laid the groundwork for a revolution in psychiatry as it turned from psychoanalytic work on the unconscious mind to pharmacological treatments of the synaptic brain. The sense of possibility was as vast as it was checkered. Psychopharmacology had only just begun to unlock the human potential, expand the mind, transform personalities, enhance capacities, alleviate mental illnesses, and provide authorities with tools for mind control. As both participant observer and prophet of this budding field, British writer Aldous Huxley shared in this optimism when, in 1958, he wrote: "Biochemistry and pharmacology are just getting into their stride. Within a few years there will probably be dozens of powerful but—physiologically and socially speaking—very inexpensive mind changers on the market." (Huxley 1980, p. 150).

When I began to do ethnographic fieldwork in neuropsychopharmacology laboratories in the mid 2000s, expectations were running high again—although psychedelic research had had it rough for some three or four decades between the first wave of enthusiasm and the arising second. In the 1960s, a combination of public health concerns, conceptual and methodological changes in psychopharmacological research, and the politicization of psychedelics in the clash between counterculture and state institutions led to their prohibition and the breakdown of psychedelic research. The current revival of psychedelic science got under way in the 1990s, which US President George H. W. Bush had announced as the "Decade of the Brain." (Dyck 2008; Giffort 2020; Langlitz 2012b) Drug researchers were hoping that the very tangible advances in their understanding of the central nervous system would translate into a second revolution in psychopharmacology. At the same time, bioethicists were raising alarm that future drugs would pose unprecedented ethical dilemmas. Rational drug design would eliminate all side effects and trade-offs, and people would take pills to feel better than well, irrespective of social conditions, or they would use novel nootropics for the purpose of brain doping in a cognitive rat race to the top in relentlessly achievement-oriented societies. At the time, social researchers studying the neurosciences sought to deflate both hype and alarmism,

but one needed fine ears and good rapport to pick up the self-doubts that had come to plague psychopharmacologists.

After completing a book on the preclinical phase of the revival of hallucinogen research around 2010, I turned my ethnographic gaze to very different areas in the behavioral sciences, and so I was most surprised that, by the time I looked again, the field had changed beyond recognition in less than a decade. Psychopharmacology had come to experience something akin to the downcast mood on those "blue Mondays" and "suicide Tuesdays" known to serotonin-depleted ravers after the ecstasies of an MDMA-fueled weekend. Around 2010, major pharmaceutical corporations decided to cut their losses. While mental health problems continued to be on the rise all over the globe, they withdrew funding from their neuroscience and psychopharmacology departments (Dumit 2018; Rose 2019, pp. 116–133). Psychopharmacology had lapsed into a deep crisis of belief in itself.

At about the same time, however, the revival of psychedelic research—a previously marginalized domain of psychopharmacology—picked up steam. Most research in this once promising field had come to a halt by the early 1970s after LSD and other hallucinogenic drugs had been prohibited. In the 1990s, a new generation of researchers used the enthusiasm surrounding all things neuro to bring back these ostracized drugs into mainstream science and thereby, they hoped, society. During the first two decades of the psychedelic renaissance, most trials remained preclinical, establishing drug safety, basic pharmacological properties, and psychotropic effects in animals and healthy humans (Langlitz 2012b). In the 2010s, however, this changed dramatically as clinical trials progressed from phase I to phase II to phase III. After reviewing the first data in 2017, the US Food and Drug Administration (FDA) designated MDMA-assisted psychotherapy of post-traumatic stress disorder (PTSD) a "breakthrough therapy," accelerating its path to registration as a medicine. In 2018 and 2019, psilocybin-assisted psychotherapy of treatment-resistant depression and major depression followed suit (Aday et al. 2019, 2020). About half of all breakthrough therapies eventually obtain market approval, which makes the designation one of the most promising paths of expedited drug development. By 2021, approximately six hundred pharmaceutical start-ups had begun to compete over an emerging market (Leonard Pickard, personal communication), which they hope will open from 2023 onward when regulatory agencies might approve the first medical applications of psychedelic and entactogenic drugs (see also https://psilocybinalpha.com/psilocybin-stocks-shroom-stocks). While large swaths of psychopharmacology are only slowly recovering from their epistemic blues, psychedelic research is experiencing a true gold rush.

The bet on psychedelics is hardly the only response to the crisis of psychopharmacology. The most prominent reaction has been the evasion movement away from the development of new drugs to better use of the digital technologies already at hand for the purpose of mental health care (Dobbs 2017; Pickersgill 2019). But the turn to psychedelics reflects a response *within* psychopharmacology that has excited the psychopharmacological imagination like no other. It reflects some broader trends in the field such as the turn to computational pharmacology. After all, psychedelic research has been thoroughly mainstreamed and can, at least to some extent, be studied ethnographically as a psychopharmacological microcosm that sheds light on

what has happened at the macrocosmic level since the field lapsed into crisis. That said, psychedelic research also continues to pose challenges and opportunities that many perceive as unique. It is these unique characteristics that are driving some of the innovation in this field and fuel the optimism of investors and researchers alike.

This article focuses on three of the most interesting responses to the problematization of psychopharmacological research and development that are currently on display in psychedelic research: first, the resumption of pharmacopsychotherapy as a half-century old but previously marginalized and even prohibited therapeutic practice; second, the continuation of self-experimentation as a simultaneously repressed and revitalized method of drug development, presumably the most ancient approach to learning about psychotropic drugs there is; third, the advent of in silico drug design as a cutting-edge approach currently used to create novel non-psychedelic psychedelics that reduce psychiatric symptoms without any mind-altering effects. Each of these responses articulates its own imaginary of innovation, which Pfotenhauer and Jasanoff (2017) propose to study in a diagnostic fashion: the imaginaries speak to how drug researchers and psychiatrists judge the undesirable present state of their field and chart more desirable futures—although there is disagreement over where the field should be heading. For an anthropology of the contemporary world but also anyone concerned about the future of drug development, one of the central questions raised by these imaginaries is whether successful psychopharmacological innovation takes the form of a modernist break with the past or of an amodernist recombination of the new with the old.

The crisis of psychopharmacology reassembles old and new figures of the human

Around 2010, psychopharmacology ran out of steam. At least that's how many of the biggest US-, EU-, and Japan-based pharmaceutical corporations saw it when they decided to downsize or even close their neuroscience departments and let their drug discovery pipelines run dry (Miller 2010). Since the 1990s, concerns about an "innovation deficit" had plagued the pharmaceutical industry at large (Drews and Ryser 1996). Historian of science Gaudillière (2021) attributes the declining productivity of research and development to the exhaustion of the postwar regime of pharmaceutical innovation that that has tied screening for promising molecules through laboratory tests and clinical trials to the marketing of these drugs. Yet drug development for disorders of the central nervous system came up against a number of specific problems that form the background of this article. The problem was not that demand for psychiatric medications had waned—quite the opposite. The World Health Organization had identified mental illnesses and substance use disorders as the leading causes of disability worldwide and more than 20% of US Americans used psychiatric drugs regularly (Whiteford et al. 2013). While it was widely recognized that the existing medications treated the symptoms, not to speak of the causes, of these conditions only partially, research and development of more effective compounds had been slow, much too slow, in the eyes of pharmaceutical corporation managers. Some observers considered the antidepressant fluoxetine (Prozac) the last

genuinely new drug that had been discovered in 1972, some four decades earlier (Greenberg 2013). All that had come out of psychopharmacological R&D since then were so-called me-too drugs that slightly modified existing molecular structures that are "no more than variations on very old themes" (Hyman 2013, p. 3) to get new patents without significantly improving efficacy. On the face of it, this was a massive failure of product innovation. Not just external critics but even key figures in biological psychiatry saw it that way, including Steven Hyman and Thomas Insel, the last two directors of the US National Institute of Mental Health (NIMH) (Miller 2010; Rose 2019, pp.116–132; but see Huskamp 2006 for a defense of me-too drugs). As moderns, they expected that the present would set itself apart from the past by surprising them with something genuinely novel.

What had disillusioned these prominent psychiatric researchers was that, in their field, the development of new drugs was not just woefully slow but also aimless. Psychopharmacologists lacked robust theories that could explain what caused psychiatric disorders and suggest how to intervene in the underlying disease mechanisms. As Hyman (2013, pp. 6–7) noted, the idea of back-engineering disease mechanisms from drug action had turned out to be wrong-headed: "Even if drugs that block dopamine receptors treat psychotic symptoms, it does not follow that the fundamental problem is excess dopamine any more than pain relief in response to morphine suggests that the original problem is a deficiency of endogenous opiates." Sociologist Rose (2019, p. 128) discerned the anthropological consequences of this theoretical vacuum: "The vision of the 'synaptic self' is fading before our eyes." It had been this waning conception of the human that had so far guided research and development of novel psychopharmaceuticals.

The modernist trope of crisis suggests that the old is dying while the new cannot be born. Although the reigning paradigm of biological psychiatry has collapsed, no successor paradigm has taken its place. The various attempts at overcoming this crisis of psychopharmacology take the form of highly technical controversies over drug development and alternative forms of mental health care, but they also reflect a struggle over what form the human will take after the demise of *Homo cerebralis* (Hagner 2000). While stories about the births and deaths of different figures of *anthropos* satisfy their readers' narrative expectations, they rarely do justice to the persistence of supposedly superseded figures that linger on, displaced by but coexisting with the new arrivals, often entering unexpected mésalliances with their now more alluring competitors.

Diagnosing a crisis means seeing a fork in the road, which calls for a decision on how to proceed. In this crisis, the most prominent decision was taken by the American neuroscientist and psychiatrist Thomas Insel who, in 2015, quit his job as director of NIMH to join the life science division of Google X. He had concluded that psychopharmacology had proved a dead end and that the future of psychiatry lay in digital technologies (Dobbs 2017). In this new framework, psychiatric patients ceased to be "neurochemical selves" (Rose 2003) and became "users" (Stadler 2013) who weren't simply their brains but extended their unwell minds to smartphone apps and other gadgets, hoping to find mental health in their relation to these technological objects. Today, we see companies like atai Life Sciences combining digital therapeutic apps with drugs like ketamine to treat depression (atai Life Sciences 2021).

Other prominent voices like that of neuropsychopharmacologist Fibiger (2012) called for more basic neuroscience, hoping that eventually it would mature enough to provide the theoretical orientation necessary for rational drug design. Former NIMH director Hyman (2013) hoped that advances in psychiatric genetics would facilitate the development of new drugs. Here, a neuromolecular gaze remained intact and guided future research. But, for the time being, it would be academic research working toward a new conception of the human mind-brain that would have to enable more effective therapeutic interventions before industry would get involved again. Psychiatrist Klein (2008) who had lived through the so-called Golden Age of psychopharmacology considered a revitalization of serendipity but recognized that recreating institutions in which psychiatrists would have more time again for clinical observation of their patients and the effects of their treatment regimes remained a utopian fantasy (instead he proposed an alternative research design to randomized placebo-controlled trials that stood a better chance of picking up therapeutic efficacy in subpopulations of patients).

In this bleak and broken landscape, a few actors glimpsed what appeared to them like a different turnoff. "One notable bright spot is with innovation and development of psychedelic therapy," wrote pharmaceutical scientist Wallach (2021). This article examines how psychedelic R&D has responded to the crisis of psychopharmacological product innovation through process innovation and, in some instances, process *re-innovation* (Freeman 1974). As actors have developed different understandings of what deficits in innovation processes have led to the dearth of new and more efficacious treatments of psychiatric disorders, their efforts to overcome this impasse are guided by different "sociotechnical imaginaries" that project better futures for psychopharmacology and mental healthcare (Jasanoff 2015).[1]

Pharmacopsychotherapy: resuming a marginal practice

The different responses to the crisis of psychopharmacology co-constitute a problematization that contains multiple possibilities of thought and action (Rabinow 2003, pp. 44–49). Following the lead of Michel Foucault, philosopher Hubert Dreyfus and anthropologist Rabinow (1982, p. 261) suggested that ways out of culturally deadlocked situations could occasionally be found not in radically new or different domains but in already existing yet marginalized practices. One of the responses to the problematization of psychopharmacological R&D was to revive psychedelic-assisted psychotherapy, an approach that had been developed in the 1950s (Dyck 2008). However, when, in the 1960s, randomized placebo-controlled trials emerged as the gold standard of psychopharmacological research, psychedelics, possibly

[1] In the context of the psychedelic renaissance, Schwarz-Plaschg (2022) points out that the sociotechnical imaginaries blossoming in the biomedical realm are not the only "socio-psychedelic imaginaries" that are informing the integration of psychedelics into American society. This article is neither concerned with decriminalization and legalization of psychedelics nor with their sacramental use. It focuses on what Schwarz-Plaschg calls the biomedicalization imaginary.

because of the widely recognized context dependence of their effects, did not fare well and their scientific investigation lost momentum (Oram 2018). Shortly after, regulators responded to a mix of public health concerns and the political turmoil surrounding the psychedelic counterculture by placing this class of drugs in the most restrictive schedule reserved for substances that lack safety even under medical supervision, show high abuse potential, and have no accepted medical use (Dyck 2008, pp. 101–118; Langlitz 2012b, pp. 24–38; Novak 1997). By the mid 1970s, most psychedelic therapy was driven underground—even though a very few therapists were able to continue their work in the licit sphere in Germany, Switzerland, and the Netherlands (Leuner 1994; Passie 1997; Snelders and Kaplan 2002; Gasser 1997). What seemed like a dying tradition in the history of mental health care has recently given a fresh impulse to psychopharmacology and psychiatry.

At first glance, the return to a pre-existing drug application might appear like a minor innovation that lacks the fascination of radical technoscientific novelty (even if it is important to stress that many new technologies and practices recombine elements of traditional ones; Michael and Rosengarten 2013, pp. 49–53). While the combination of psychotherapy with antidepressants has become normal in the treatment of mood and anxiety disorders, such pharmacopsychotherapy requires daily administration of the drugs rather than a few well-prepared psychedelic sessions and it does not foreground the drug-induced experiences in the psychotherapeutic process (Greenway et al. 2020). Clinically, the available antidepressants often fail to bring lasting relief and, to the extent that they are efficacious, their therapeutic successes are paid for with significant side effects. Therefore, psychedelic-assisted psychotherapy has been presented as a full-blown "paradigm shift in psychiatric research and development" (Schenberg 2018). One psychiatrist presented the approach as a way of overcoming the limitations of existing pharmacotherapy *and* psychotherapy (Mithoefer et al. 2016). Other researchers emphasized that it did not repeat the mistakes of an "oversimplified neurobiological approach" but did justice to the complexity of psychiatric disorders (Ona and Bouso 2019). The Brazilian neuroscientist Eduardo Ekman Schenberg, founder of the start-up Phaneros that conducts research and offers clinical training in psychedelic-assisted psychotherapy, conceived of this approach as a way out of the crisis of psychiatry. Following the sociologist Nikolas Rose's diagnosis, he conceived of it as a triple crisis of therapeutics, diagnostics, and etiological explanation (Rose 2016). Psychedelic-assisted psychotherapy addressed all three dimensions, Schenberg argued. Therapeutically, it did not rely on daily administration of drugs to counter a persistent neurochemical imbalance but induced an experience with long-term mental health consequences. Diagnostically, the approach challenged a nosology that discriminated discrete and mutually exclusive disease categories. In line with the Research Domain Criteria (RDoC) approach that the US National Institute of Mental Health had developed in response to the crisis, Schenberg conceived of psychiatric disorders as organized along continuous spectra, growing out of disruptions of the normal range of operations in broad domains of dysfunction common to all psychopathology (see also Tricklebank et al. 2021, pp. 1419–1420). This new nosology could accommodate the treatment of different disorders such as depression and drug dependence with one and the same psychedelic drug (see also Carhart-Harris and Friston 2019,

pp. 320–321). In contrast to RDoC, however, which understood the dimensions of psychopathology in strictly neurobiological terms, Schenberg (2018, p. 5) attributed psychiatric disorders not to brain dysfunctions but to "mental injuries," which psychedelic-assisted psychotherapy could treat "holistically." Its resurgence partially wound back the transition from psychological to biological conceptions of the human in psychiatry (Rose 2007, p. 26).

In the 2010s, at about the time when neuropsychopharmacology lapsed into crisis, the first clinical trials since the breakdown of psychedelic research some forty years earlier tested psychedelics for a number of indications, most importantly psilocybin and LSD for the treatment of anxiety associated with life-threatening disease (Gasser et al. 2014; Griffiths et al. 2016; Grob et al. 2011; Ross 2018), psilocybin and ayahuasca for the treatment of depression (Carhart-Harris et al. 2016; Carhart-Harris et al. 2021; Davis et al. 2020; Palhano-Fontes et al. 2019), and MDMA for the treatment of PTSD (Mitchell et al. 2021; Mithoefer et al. 2011; Mithoefer et al. 2019; Oehen et al. 2013). This led to the FDA's Breakthrough Therapy designations for MDMA- and psilocybin-assisted therapy of PTSD and depression. Upon completion of phase 3 trials, about half of the clinical programs on this expedited review path have gone on to receive market approval, which, in the case of MDMA, might happen as early as 2024, and psilocybin could follow suit shortly after. The European Medicines Agency (EMA) has also approved MDMA and psilocybin for clinical trials to determine whether psychedelic-assisted psychotherapy will be (re-) introduced in the European Union, which led some researchers to speculate that this integration of pharmacological and psychotherapeutic intervention could usher in "a new era in psychiatry." (Nutt 2019; for a critical assessment of such promissory psychedelic science, see Noorani and Martell 2021).

What is striking about the ongoing approval processes is that they steadfastly ignore these claims to novelty by continuing to assess the pharmacological intervention while taking no account of the psychotherapeutic intervention, which it serves (Langlitz 2015; Noorani and Martell 2021, p. 3). If regulators were to evaluate psychedelics as adjuncts to psychotherapy, they could not base their decision-making on randomized placebo-controlled trials alone but would have to control for the administered psychotherapy as well (one model for this would be so-called culture-controlled trials; Wallace 1959). While a commentator in the *Journal of Psychopharmacology* remarked that "it may be helpful if studies of hallucinogens are not thought of as drug studies at all, but as psychological treatment studies" (Goodwin 2016), neither the FDA nor EMA are responsible for the assessment of new psychotherapies and the psychedelic organizations applying for their approval have no interest in further complicating the process by emphasizing that they do not believe that psychedelics are therapeutic in their own right but that they function as catalysts of psychotherapies. These psychotherapies have been outlined in treatment manuals but remain black-boxed in the approval process.

They are not black-boxed in the internal discussions of the research groups and companies that run the clinical trials though. While initially calls for more systematic investigations of set and setting mostly came from social researchers who got involved in the revival of psychedelic research (Langlitz 2012a; Hartogsohn 2016), neuropsychopharmacologists such as Carhart-Harris et al. (2018) have recently

begun to draw attention to the extrapharmacological factors that shape drug action in the case of the highly context-sensitive psychedelics (but maybe also in the case of other classes of drugs; see Alexander et al. 1978; Wallace 1959; Zinberg 1984). This could have significant implications for rational drug design, which might profit from including the context of drug administration. In fact, at least one start-up company, Eleusis Ltd., already works on a care delivery platform to realize the therapeutic potential of psychedelic-assisted psychotherapy by not only developing new drug candidates but also the setting, in which these drugs would be given to patients (https://www.eleusisltd.com). Eleusis addresses the crisis of psychopharmacological R&D by extending their conception of development from pharmacological agents to contextual factors that co-determine their effects. This extension of rational drug design to extrapharmacological factors that shape drug action represents a case of process innovation in response to the crisis of psychopharmacological R&D. More generally, it could be said that the budding psychedelic industry is very much invested in developing settings that contain the immense experiences induced by psychedelics. Its economic viability depends on preventing the kind of uncontrolled spillover of LSD from a Sandoz laboratory into Western societies at large, which had put an end to the first wave of psychedelic research (Noorani 2021). The imaginary of innovation that inspires the turn to psychedelic pharmacopsychotherapy assumes that psychiatry and even psychopharmacology had been too focused on the invention of pharmaceuticals and had neglected the invention of sociocultural milieus and practices that work synergistically with pharmaceuticals old and new to produce a combined effect that is greater than what pharmacotherapy or psychotherapy could achieve on their own.

Self-experiments in the discovery of novel psychedelics

Working on this article I texted with a psychopharmacologist, to hear what he thought about some of the proposals for how to overcome the crisis of psychopharmacological research and development: creating more valid animal models of psychiatric disorders, using systems neuroscience approaches, identifying molecular targets via genomic analysis, etc. (Tricklebank et al. 2021). He responded: "Frankly, I think the only thing that works is to try out the drugs like in the sixties… without the whole regulatory overkill."

In hindsight, drug research in the 1960s was wild: self-experiments were not out of the ordinary and patients, especially mental patients, were often given new drugs without informed consent or any other form of ethical review process. Both curiosity and recklessness went unchecked, at least by contemporary standards. However, the 1960s were also the time when all of this began to change, when protocols and policies began to multiply, regulatory oversight came to be extended, and Institutional Review Boards (IRBs) were established to protect patients and curb researchers (Rothman 1991; Stark 2012). Eventually, this protection also covered employees of research universities and pharmaceutical companies who were not supposed to participate in unauthorized drug trials, even if they wanted to test a drug they had invented on their own body and mind. They had come to be seen as "vulnerable

human subjects" on a par with mid-twentieth century participants in clinical and preclinical trials who, from the 1970s onwards, had come to be seen as victims of scientific exploitation (Campbell and Stark 2015). While the practice of self-experimentation is usually not expressly prohibited, a microphysics of power involving reputational damage (Forstmann and Sagioglou 2021), promotion and funding decisions, and lack of respected publication venues makes sure that, today, scientists no longer speak in public about their self-experiments, if they still take the risk of experimenting on themselves at all.[2] As the knowledge culture of psychopharmacology grew more rigorous, both ethically and epistemically, it also grew more rigid, leaving less space for researchers to follow their hunches.

In 2006, while doing ethnographic fieldwork on the renaissance of hallucinogen research at an animal laboratory at the University of California, San Diego, I attended a symposium discussing future directions in the chemistry of the mind sponsored by the pharmaceutical start-up Acadia. The company had invited three luminaries of psychopharmacology: Swedish Nobel Prize laureate Arvid Carlsson, Oxford professor Leslie Iversen who had directed one of Merck's industrial drug development units that would soon be closed down in the wake of the R&D crisis, and the Russian-American underground chemist Alexander "Sasha" Shulgin who had invented more that two hundred new psychedelic drugs in a small wooden shack on his farm, testing every single substance on himself, his wife, and his friends. In a Q&A session after their presentations, Shulgin claimed that animal experiments could not determine the psychedelic potential of a novel compound because disruption of conditioned responses or changes in motor-activity didn't tell investigators which "door of perception" the drug might unlock, that is, which psychospiritual lesson users could learn from it. In other words, self-experimentation was a necessary element in the development of new psychedelic drugs, especially if they were to be used as catalysts of psychotherapy.

Acadia's president Mark Brann jumped in to give some historical context to the students attending the event: "What people don't realize is that what Sasha did was extraordinarily common in the 1960s and'70s. When people were testing compounds to investigate drug structure/activity relationships …, they would taste the drugs themselves. … The pharma industry, up until the mid-'70s, knew this was occurring and that it was very facilitating of the drug programs. The perception was that people knew they were taking a risk; they were curious about the results; they were dedicated scientists who wanted to see progress, and they did it." (Langlitz 2012b, pp. 168–169) In the mid-twentieth century, not only industrial scientists but also researchers at US federal institutions such as the National Institute of Mental Health practiced and were even expected to practice self-administration of psychotropic drugs to understand their effects on a person's interiority, specifically

[2] In psychedelic-assisted psychotherapy, the taboo surrounding the therapist's personal experience with illegal psychedelic drugs (which may or may not be self-experimental in the strict sense of the word) puts a strain on the patient-therapist relationship and has stifled research on how the extrapharmacological factor of the therapist's experience impacts treatment success, argued the psychotherapists Nielson and Guss (2018).

on perceptions and emotions, before administering the drug to test subjects. Science studies scholars Stark and Campbell (2018) emphasize that, at the time, many researchers regarded their own interiority not as a problem but as a resource that could further the process of knowing the mind–body experiences of others (see also Solhdju 2011; Stark 2012, p. 91).

Although Brann recognized the value of self-experimentation for drug development, he also made it clear that times had changed. Acadia was operating in what he called a "liability culture," in which the research of individual employees was a collective responsibility of the company. "If someone [conducted a self-experiment] in my company, we would immediately terminate them because of the exposure they would create for our efforts. Now that we are in an environment where each step in drug development is hyperregulated, if such an activity occurred it would expose the company." (Langlitz 2012b, p.169).

Sociologists of science Abraham and Reed (2002) have contested the claim that regulation of pharmaceutical research hinders scientific discovery and innovation. But, at least in psychopharmacology where animal behavior assays have proved poor predictors of clinical efficacy, many researchers I have spoken to expressed in off-the-record conversations the sentiment that the increasing repression of self-experimentation is holding them back. Having done long-term ethnographic fieldwork in drug research labs over more than one and a half decades, I have observed first-hand how researchers' latitude has shrunk. In the mid 2000s, I witnessed and was allowed to write about so-called pilot studies at the University of Zurich, which researchers used to obtain personal knowledge of a substance, its dosage, and the experimental setting in which it would eventually be administered to test subjects (Langlitz 2012b, pp. 109–113). It was understood that one operated in a gray area, but nobody seemed especially concerned about repercussions. By 2010, the university had made it clear that it would no longer tolerate the practice of self-administration. It began to enforce its prohibition, not just for controlled substances like psychedelics but also for registered medicines, not to speak of entirely new and unknown molecules like Shulgin's. From a historical review of self-experimentation with psychoactive substances, psychiatrist Torsten Passie concluded that "the great times of undertaking controlled [self-experiments] appear to be over." (Passie and Brandt 2018, p. 35).

As a result, it was no longer possible to try out an idea for an experiment before going through the hoops of an IRB application and, depending on the national organization of drug research, approval from regulatory authorities on the state level. In the case of novel psychoactive substances, lengthy and expensive drug safety studies in animals would also be required before administering an unknown drug to a human being, even if this human being was the inventor of the drug. Such investments of time and money only made sense if one already knew that publishable or marketable results were likely. An adverse effect of incentivizing researchers to play it safe in terms of their own bodily and mental health is that they are also incentivized to take less intellectual risks and not to treat psychopharmacological research as serious play, however, creative such a ludic attitude toward scientific discovery might be (Langlitz 2019b).

Thus, I was surprised when I first heard about an academic research group developing new psychedelic drugs that claimed to receive funding from industry precisely

because their industry partners knew that they were testing their compounds on themselves (while this practice remained a taboo topic in the lab's academic milieu). At the time, competition between a quickly growing number of psychedelic start-up companies grew fiercer. Many corporations were interested in the development of novel drugs that could be patented, had shorter half-lives and thereby enabled shorter and cheaper therapy sessions, or were experientially less challenging for patients (opening new doors of perception was not of central commercial concern). Collaborating with researchers who did not exclusively rely on costly and time-consuming animal experiments but obtained first-hand knowledge of their creations over the weekend and for free before they embarked on the long journey to eventually recruiting test subjects for a preclinical trial gave these companies an advantage over their competitors.

However, it is important to note that, in this emergent research environment, self-experimentation played a much more limited role than in Shulgin's enterprise. The self-experimenting head of the academic laboratory that I interviewed—let's call him Richard Roe—primarily saw the value of self-experimentation in determining potency, onset, duration, side effects, and some basic psychopharmacological properties (e.g., involvement of the visual system, but not whether a compound conjured up more childhood memories). Roe remained skeptical of phenomenological characterizations of drugs because the latter had proved highly subjective and contingent on set and setting, especially if a drug hadn't been tested by several experienced self-experimenters who had tried it many times, at different doses, and under a range of circumstances. He also argued that Shulgin's intuitions about the therapeutic value of his creations (for example, as antidepressants) could not be confirmed, maybe because Shulgin had not suffered from the psychiatric conditions in question, or because the markers that predict, say, antipsychotic action cannot easily be self-assessed. Thus, Roe's brand of auto-experimentation differed from the kind of self-administration of psychotropic drugs that Stark and Campbell (2018, pp. 800–803) have described as a "method of ingression" in that the focus was not on the relative effects of the drugs on a person's inner experience but on the drugs' objectifiable effects on a person's body. Although Roe was passionate enough about self-experimentation to take the associated risks, he did not believe that a more widespread return to this practice would be a panacea to resolve the multiplex crisis of psychopharmaceutical innovation. For this, too many other factors also thwarted the process. That said, Roe was convinced that drug discovery could be reinvigorated if self-experimentation resumed a central role in neuropsychopharmacological research and development. Here, too, product innovation was facilitated by process innovation, or, really, process *re-innovation*: by resuming an old way of testing new drugs, Roe's laboratory hoped to move beyond one of the roadblocks that had hamstrung the field.

The imaginary underlying the return to self-experimentation saw psychopharmacology as swaddled in intellectually suffocating red tape. Policies and informal norms dissuading researchers from trying out novel compounds on themselves crossed out the *psycho-* in *psychopharmacology*. To make psychopharmacology innovative again, curiosity about how different drugs changed not just the brain but also the mind would have to roam more freely than it did under present

circumstances. Drug research would have to become an experiential science once more.

The question is how common such self-experimentation is and how this could be determined, given regulatory and legal pressure on the practice. From ethnographic experience, I conjecture that it is widespread in psychedelic research. This does not mean that it is also widespread in psychopharmacological R&D at large. Survey data on auto-experimentation suggests that 10–20% of clinical psychiatrists in France try the medicines they prescribe but says nothing about research scientists in academy and industry (Bernard and Dessomme 2020). Here, an anonymized survey and in-depth ethnographic work based on relations of trust would provide more clarity.

It should be noted though that the epistemological significance of the research practices of Shulgin and Roe does not hinge on how representative they are of their field. Marginal practices are worth investigating precisely because more common mainstream practices have led into a cul-de-sac. Understanding self-experimentation today can serve a diagnostic purpose as it sheds light on the deficiencies of psychopharmacological research and development that it is meant to compensate.

It should also be noted that, even if the epistemology of self-experimentation was no longer dismissed as subjective and therefore inferior to objective testing, recreating a scientific workplace where researchers would used their own bodies and minds as resources for knowledge-making would require much sociotechnical imagination. It would require recalibrating the relationship of institutional and personal responsibility, revisiting the role of ethics committees in human experimentation, and maybe even a more comprehensive rethinking of the rationalization of ethics. What would a collectively held, institutionally stabilized, and publicly performed vision of a desirable future look like, in which employees of universities and pharmaceutical companies received official permission to take the kind of risks that Shulgin and his friends took in a relatively unregulated private space that ceased to exist in the late twentieth century?

Virtual pharmacology and the development of non-psychedelic psychedelics

While the return to self-experimentation reintroduces the oldest approach to drug discovery that has presumably taught humans about pharmacological properties of plants and mushrooms for thousands of years, there is also a high-tech response to the innovation crisis in psychopharmacology. In the 2010s, computational pharmacologists began to collaborate with software developers on technologies that allow to design new drugs in silico. In 2019, pharmaceutical chemist Brian Shoichet announced that one of the bubbles constraining novel drug discovery had popped (University of California, San Francisco 2019). The days had long passed when drug development relied on the personal knowledge and chemical intuitions of ingenious minds like Shulgin's to find new drugs in the vast and alien universe of potential compounds. Since the 1990s, pharmacologists had moved from manually testing every single substance for biological activity at a chosen biological target to high-throughput screens of a few million candidates. But this approach still only provided

access to a small fraction of chemical space estimated to contain some 10^{63} drug-like molecular structures (Gloriam 2019). Instead of screening drug libraries physically, Lyu et al. (2019) had created an ultra-large virtual library of 170 million compounds, which a computer simulation rotated and adjusted to identify those compounds that might bind to a particular receptor or some other target. A drug discovery process that used to take several years could now be completed within weeks, although it still required experienced human researchers to eye-ball high scoring compounds and pick the most promising ones for physical testing. Most of these substances have never actually existed but they could be made on demand. Reminiscent (at least in aspiration) of Jorge Luis Borges' Library of Babel, which houses books that contain every possible ordering of the basic characters, these virtual libraries represent a space of molecular potentialities that by far exceeds the human imagination (even though they still only cover a fraction of chemical space) (Borges 1998 [1944]). In the history of pharmaceutics, this is process innovation writ large.

In 2020, Shoichet's laboratory at the University of California, San Francisco, provided a proof of concept that in silico drug design allowed to discover new drugs. Looking for a medication to treat sleep disorders and jet lag, they searched the virtual library for molecules that specifically docked to one of the two mammalian melatonin receptors called MT_1. They ran computer simulations of 72 trillion drug-receptor interactions and eventually identified 40 potential drugs. Employing another recently invented technology, the Ukrainian company Enamine was then able to synthesize 38 of these molecules by combining prefabricated chemical building blocks with one another (at a cost of approximately $100 per molecule). At that point, in vitro and in vivo testing allowed Shoichet's group to identify those drugs that actually bound to MT_1 and to establish their behavioral effects in mice (Stein et al. 2020). The chemical scaffolds of these molecules were unrelated to known melatonin receptor ligands. Thus, virtual pharmacology had helped to discover drugs that, structurally speaking, were no me-too drugs. Shoichet's lab had shown that computer-aided drug design could help to invent genuinely new psychotropic substances. Whether this new paradigm for R&D can show a way out of the ongoing crisis of psychopharmacology will depend on whether these substances will also turn out to be clinically efficacious in patients. For now, they have only elevated the mood of pharmacologists.[3]

In light of the promising results of psychedelic-assisted psychotherapy, Brian Roth's laboratory at the University of North Carolina at Chapel Hill received a

[3] One major reservation regarding Roth's approach to drug discovery was raised in a personal communication with Hamilton Morris: "Roth's ULTRA-LSD* technique is designed to characterize high affinity ligands, which are then further screened for functional activity and receptor selectivity. Neither affinity nor selectivity are in and of themselves a determinant of therapeutic efficacy. These techniques would fail to recognize most of the psychedelics considered most important for their therapeutic effects, which often possess neither high affinity nor selectivity. LSD has high 5-HT2A affinity but very low selectivity. Psilocybin has high 5-HT2A affinity and low selectivity. Mescaline has such low affinity for 5-HT2A that it would likely be considered inactive via in vitro assays if it weren't for its known history of human use. I don't mean this as a criticism of Roth's work, I think what he is doing is totally brilliant. But concepts like affinity and selectivity, while extremely valuable in pharmacology research, are not immediately applicable to a therapeutic domain especially in the realm of psychedelics."

$27 million grant from the US Department of Defense to use the tools of computational pharmacology to develop drugs that have the therapeutic but not the psychedelic effects of 5-HT_{2a} agonists like LSD and psilocybin. Facing a mental health crisis among American soldiers (with more than 20 suicides per day), the Pentagon recognized the potential of psychedelic drugs but considered the psychedelic experience an "intolerable, deleterious" side effect that would make administration too difficult and time consuming in the vast system of Veterans Affairs medical facilities (quoted in: Yakowicz 2021). Similarly, the American business magazine *Forbes* cited a healthcare analyst who explained that psychedelic-assisted psychotherapy could not be mainstreamed unless the drugs were rid of their hallucinogenic properties because too many patients were afraid of experiencing altered states of consciousness and they should be able to take their medications at home instead of requiring a costly psychotherapeutic setting (Yakowicz 2021). The mind-altering effects of psychedelics appeared to stand in the way of scaling up their clinical applications as medicines.

And so began the quest for so-called psychoplastogens that bind to 5-HT_{2a} receptors like the classical psychedelics but only activate the neural pathway mediating the antidepressant and anxiolytic effects of psychedelics recently demonstrated in clinical trials without also activating the hallucinatory pathway responsible for the visionary experiences that had shaped the public image of psychedelics. Using the toolkit of traditional medicinal chemistry, David Olson's laboratory at the University of California at Davis developed the psychedelic 5-Meo-DMT into the supposedly nonpsychedelic 6-Meo-isoDMT, which enhanced neuroplasticity without inducing a head-twitch response in mice. In the absence of self-experiments, murine head twitches were taken as an indicator of hallucinogenicity (Dunlap et al. 2020; Halberstadt et al. 2020). Subsequently, virtual pharmacology allowed a consortium of several laboratories, including those of Roth and Shoichet, to discover and test on animals a series of compounds also believed to be nonpsychedelics psychedelics. Modeled on LSD as it docks to the 5-HT_{2a} receptor, two 5-HT_{2a} receptor ligands, (R)-69 and (R)-70, showed antidepressant-like actions in mouse models of depression and anxiety without a head-twitch response in mice (Kaplan et al. 2022). But, since no self-experimental reports on how drugs like 6-Meo-isoDMT, (R)-69, and (R)-70 affect the human mind have been published and preclinical human trials are still far off, it is not certain whether these drugs are actually free of psychedelic effects, and if they would be clinically efficacious.

The development of such psychoplastogens led to a scientific controversy over the role of the psychedelic experience in pharmacopsychotherapy. This new direction in psychopharmacological research and development was opposed by researchers who advocated another 'new' paradigm, or really the revival of an old but marginalized paradigm, namely the use of psychedelics to catalyze psychotherapy. Roland Griffiths' group at Johns Hopkins University argued that the subjective effects of psychedelics, especially mystical-type experiences, but also meaningful insights and

belief changes, were necessary for their enduring therapeutic effects—a view echoed by others in the research community (Majić et al. 2015; Roseman et al. 2018). Integrated in a psychotherapeutic process, these experiences could serve as narrative inflection points in patients' lives that allowed them to overcome harmful patterns of thoughts, feelings, and behaviors. In light of the increasingly recognized clinical success of their approach, they saw the burden of proof on the side of those who claimed that psychedelic effects were dispensable (Yaden and Griffiths 2021).[4]

On the other side of the controversy stood the advocates of psychoplastogens. Like Roth, they based their research strategy on the assumption that alterations of consciousness could be a mere side effect and that psychedelics were proving therapeutically efficacious not because they induced mystical-type experiences but because they increased neural plasticity. This camp acknowledged Griffiths' finding that clinical improvements *correlated* with the intensity of mystical-type experiences but pointed out that correlation did not prove causation (Olson 2021). In this controversy, the psychoplastogen camp used both traditional and the very latest drug discovery technologies to defend a therapeutic model that continues to rely first and foremost on the effects of drugs rather than the psychotherapeutic integration of drug experiences. What sets its approach apart from the exhausted and disproven explanatory model that had led psychopharmacology into crisis was that it does not rely on correcting neurochemical imbalances but on inducing a neuroplastic reorganization of particular neural circuits (Olson 2018).

The controversy pits against each other two responses to the problematization of psychopharmacological drug development: one uses 5-HT_{2a} agonists to intervene in a mechanism in brain functioning that, until then, had not been deliberately targeted, namely circuit-specific neuroplasticity; the other uses 5-HT_{2a} agonists to intervene in psychological processes by resuming a form of psychotherapy that works through psychedelic experiences to alter people's attitudes toward themselves, others, and the world. Both camps presuppose that the neuroplastic effects of psychedelics play a significant role, but pharmacopsychotherapists believe that enhancing neuroplasticity is not sufficient to restore mental health, that it also takes an experience so powerful that patients come to see their whole lives with new eyes, an experience that, if properly integrated through psychotherapy, can lead patients to change their ways.

What, at first glance, looks like a disagreement between specialists over the future of their field reflects a deeper anthropological disagreement. Bryan Roth holds out the prospect that non-psychedelic psychedelics will enable an advance in psychiatry so huge that it will "transform humanity" (quoted in: Yakowicz 2021)—and, if the prevalence of mental illness in the global population is as high as many epidemiologists think it is, and if Roth's new drugs were as effective as he hopes they will turn out to be, then humanity would indeed be transformed as large numbers of

[4] It should be noted, however, that there the field of psychedelic-assisted psychotherapy features a more diverse range of psychotherapeutic approaches, from psychoanalysis to Acceptance and Commitment Therapy and from Internal Family Systems Therapy to Cognitive Behavioral Therapy. And there are also researchers like Matthias Liechti who believe that the therapeutic effect of psychedelics does not require their application in a psychotherapeutic context.

people became significantly healthier. Although pharmacopsychotherapy also aims at reducing symptoms and restoring psychological normalcy, its focus on transformative experiences might have further ramifications for how people conceive of the human place in the cosmos. After all, mystical-type experiences temporarily dissolve or minimize the ego and make its concerns appear less salient in the face of an infinitely larger universe. If many more people experienced this change in perspective, it would also transform humanity, in this case by transforming people's self-conception. Here, the transformation would not just be about psychophysiological normalization of the global population but about a change in anthropology, understood quite literally as the *logos* of *anthropos* and the corresponding epistemic and therapeutic practices (Rabinow 2008, p. 14). At the end of the day, the debate over how to overcome the crisis of psychopharmacological research and development is also a debate over changing and competing conceptions of the human.

These conflicting anthropologies inform conflicting imaginaries of innovation. As discussed above, the proponents of pharmacopsychotherapy see the future of psychiatry in the development of hybridized forms of treatment that integrate consciousness-altering drugs and psychological interventions while the proponents of psychoplastogens set their hopes on the development of a novel class of drugs that does not alter consciousness, at least not acutely, but enables a rewiring of the brain to restore normal affect, cognition, and behavior. Virtual pharmacology projects an sociotechnical imaginary that views the minds of medicinal chemists like Alexander Shulgin as only capable of representing such a negligible slice of all possible substances that their half rational, half intuition-driven design of new mind drugs needs to give way to much faster computer simulations that do not expand consciousness but chemical space. The resulting abundance of new drug candidates requires different methods of high-throughput screening to replace the equally cumbersome and risky process of self-experimentation (at least until the wheat has been separated from the chaff). In this scenario, the future of psychopharmacological R&D prominently features computers and other automatons that extend the scientific imagination beyond its all too human limitations.

Conclusion

This article has reviewed the most important responses to the crisis of psychopharmacological innovation in the revival of psychedelic research. Some molecular pharmacologists turn to cutting-edge computer simulations to develop structurally new compounds in silico, others have resumed the age-old practice of self-experimentation, while psychiatrists develop further the extrapharmacological psychotherapeutic context that modulates and redirects the pharmacological effects of substances that have been known for decades, maybe without recognizing their full potential. The underlying imaginaries highlight the ideal–typical opposition of modernist and amodernist approaches to innovation. The modernist imaginary relies on the introduction of brand new technologies such as ultra-large virtual libraries to leave behind the old ways and usher in a new age of drug development. By contrast, the amodernist imaginary puts its

hopes on remixes of old and new substances and practices. Although so far the resurgence of psychedelic psychiatry has mostly followed the latter model, it is often framed by the modernist tropes of "paradigm shift" (Schenberg 2018), "disruptive psychopharmacology," (Heifets and Malenka 2019), or "disruptive innovation" (the latter term has been used by Citigroup to explain why it listed the psychedelic biotech company atai Life Sciences among its top stock picks in 2021; Pham 2021).

But there is another way to think about the comeback of psychedelics, which really is a comeback. For what the neuroscientist Boris Heifets and the psychiatrist Malenka (2019, p. 776) dubbed disruptive psychopharmacology involves "compounds that have been known for quite some time in other contexts" and that, they hope, will now be developed into better therapies as "all the tools in our modern armamentarium" are applied to understanding and improving how they work in a different context. A number of cultural theorists have observed a transition in our collective experience of time that does not take the form of radical breaks with the past but of a simultaneity of elements from different historical periods that are assembled and reassembled into constantly changing polytemporal clusters (Gumbrecht 2014, pp. ix–xiv; Latour 1993, pp. 74–76). The fact that what has been will be again doesn't mean that there is nothing new under the sun (virtual pharmacology might very well be a game changer). It means that the latest additions leave in place but profoundly restructure the already existing configurations they enter (perhaps it still takes self-experimentation and psychotherapy to unlock the pharmacopsychological potential of novel psychedelics designed in silico, although the new drugs might recast these enduring practices). The story of the psychedelic renaissance fits well into such an amodernist imaginary of innovation.

And vice versa, an amodernist imaginary of innovation suits an experience frequently reported by users of psychedelic drugs: "The funny thing is that, despite all the newness, there's something about all of it that feels – well, the only way I can put it is that it's like coming home," noted Ann Shulgin, Sasha's spouse and fellow psychonaut while under the influence of mescaline-containing peyote buttons. "As if there's some part of me that already knows – knows this territory, – and it's saying Oh yes, of course! Almost a kind of remembering – !" (Shulgin and Shulgin 1991, p. 120) She was astonished to be astonished by an experience that seemed to be no more than a variation on a very old theme (see also Langlitz 2019a). This strange mixture of remembrance and wonder rather than the sense of crisis that arose in psychopharmacology about a decade ago might be the mood that best suits the revival of psychedelic research today. In contrast to the imaginary of innovation that fuels the disruption economy, in which the first generation of psychedelic start-up companies operates, it envisions the integration of psychedelics into the late modern pharmacopeia as continuous with the *longue durée* of human uses of these ancient drugs, which never fail to surprise.

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